

# Some central nutritional problems of the present time

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I FEEL GREATLY HONORED to have been chosen to give the first W. O. Atwater Memorial Lecture. Dr. Irving has just described Dr. Atwater's work as a nutrition researcher, organizer, and educator.

Reading through some of Dr. Atwater's original publications, I have been very much impressed by his scientific achievements.

Besides being an accomplished researcher, Dr. Atwater was also a great idealist, who believed that the results in the field of science influence the mental and moral as well as the physical development of man. Two sentences from his book *Methods and Results of Investigations on the Chemistry and Economy of Food*, illustrate this belief:

To replace dear food badly cooked by economical food well cooked is important for purse and health. To make the table more attractive will be an efficient means for making home life more enjoyable and keeping the father and sons from the saloon.

Our knowledge about the nutrition of man and animals is based so much on the development of chemistry that this knowledge could be increased and deepened only to the extent to which chemistry during different periods allowed. No real knowledge about the functions of food in the organism existed before Lavoisier explained the phenomenon of combustion. In 1777 he demonstrated that respiration is slow combustion, in which oxygen is consumed and carbon dioxide is formed. Eight years later, from the formation of heat by respiration, he drew the conclusion that respiration is not restricted to the combustion of carbon—also, hydrogen is burnt to water. The organism obtains the raw materials for combustion from its food.

<sup>1</sup> The W. O. Atwater Memorial Lecture was established by the Agricultural Research Service of the U.S. Department of Agriculture to recognize and encourage outstanding accomplishment in the broad field of nutrition and the sciences it embraces. W. O. Atwater (1844–1907)—a farsighted pioneer who established the science of modern human nutrition in the United States—was USDA's first chief of human nutrition research. Dr. Virtanen, winner of the Nobel Prize for chemistry in 1945, is director of the Biochemical Research Institute, Helsinki, Finland. His Atwater lecture was presented in cooperation with the American Institute of Nutrition on April 16, 1968, during the 52nd Annual Meeting of FASEB in Atlantic City, N.J.

These revolutionary results made the experimental study of the functions of food possible. As early as 1816 the French physiologist Magendie observed that the nitrogen found in the body was derived from the nitrogen compounds in the food. He employed diets of pure carbohydrates and fats to prove that food nitrogen is essential.

Mulder in 1838 gave the name protein to the nitrogenous material which he believed to be the fundamental constituent of tissues, and Magendie demonstrated by his studies 3 years later that gelatin would not replace meat protein in the diet. Thus it was observed at an early stage that the proteins have a special significance in food. Carbohydrates, fats, and proteins were then regarded as forming the groups of organic compounds needed in the food of man and animals.

After this, during the second half of the last century and until the early part of this century, nutrition research was directed toward the elucidation of the composition and digestibility of various foodstuffs of plant and animal origin, and the determination of the nutritive value of foods and the energy requirements for the various functions of the body. Thus it was possible to lay the quantitative foundation for the nutrition of man and animals.

Nutrition chemists and physiologists built during a period of half a century a doctrinal structure which made it possible to calculate on an energy basis the requirements of foodstuffs of individuals, of nations, and roughly even of the world population. The need of proteins was not more accurately known but on the basis of experience it could also be included in the calculations. All this meant an enormous achievement. Energy viewpoints dominated the world of ideas of most of the nutritionists of that time to such an extent that, figuratively speaking, the living organism was considered as a heat engine and food, protein excluded, solely as fuel.

The connection of certain special diseases, such as scurvy, rickets, and beriberi, with food was not recognized for several decades, and food was generally believed to consist solely of carbohydrates, fats, proteins,

salts, and water. All this was in spite of the fact that, for hundreds of years before, practical experience had shown this type of disease could be prevented or cured by addition of fresh vegetables, fruits, liver, and the like, to the diet, and that in Bunge's laboratory in Basel since 1880 feeding experiments with mice on purified feed had definitely demonstrated the requirements of unknown accessory factors for growth and life.

The first references to the necessity for vitamins appear late in the handbooks of well-known physiologists. For example, the large textbook of the famous Finnish physiologist Robert Tigerstedt, *Lehrbuch der Physiologie des Menschen*, which was used as the medical study book at Scandinavian and German universities, mentions briefly for the first time in its ninth edition of 1919 the mysterious substances called vitamins. Thus in the latter part of the 1800's the curious situation had been reached when the prevailing line of nutrition research ignored the observations most significant to man's health, and the experience obtained in practice.

The inadequate information had obviously some effect on the creation of such a tragic situation, but there was probably another and even more profound reason in the background. The doctrine of calories as a measure of the energy requirement and food value was scientifically well founded, the adequacy of which had been proved experimentally with both man and animals. The statements about new nutritional factors, the nature and function of which were quite unknown, were foreign to this doctrine and could not be fitted to it. The result was: better to ignore or postpone the discussion of the disturbing observations.

One wonders whether such a situation could arise in our day when research work has acquired quite another position in society than that it still had at the turn of the century, and information also has increased tremendously. I think that still, at this moment, in any field of science there exists the danger that on a line aside from the highway of research or in its periphery, scientific work is retarded or prevented due to the lack of attention and grants, although from such work significant impulses to the development of science often arise. It is important that this is not forgotten in the organizations which distribute research grants, even if such dramatic cases as the one concerning the vitamins are unusual.

The discovery of vitamins led nutrition research into a new line. Without a firm chemical foundation the elucidation of the chemical nature of vitamins and their part in the nutrition would not have been possible. The demonstration of the indispensability of certain amino acids was of similar importance. Nutrition research was now linked with biochemical research. As a result of this cooperation, vitamins could be isolated as pure chemical compounds one after another, their molecular structure determined, and most of them synthesized. These achievements made it possible to study the mode of action of vitamins and other similar compounds of low molecular weight in metabolic reactions as building stones of the coenzyme part of enzyme molecules.

At the same time the study of vitamins proceeded, our knowledge about the reaction mechanisms of aerobic and anaerobic metabolism increased. It was about 150 years after Lavoisier had demonstrated that respiration was slow combustion that this process could be shown to include series of separate enzymatic reactions, the quantitatively most important pathway being the Krebs cycle. The total energy of the combustion was thus released in small portions. This is essential for harmony of metabolism and for all life. One of the most difficult problems concerning metabolism has been how the energy released as the food is gradually broken down is utilized for synthetic processes, above all for the growth and renewal of tissues and for muscular work. Lipmann's paper in 1941, *Metabolic Generation and Utilization of Phosphate Bond Energy*, presented the solution of this problem. His idea of the storage and transfer of energy in the energy-rich phosphate bond has had a decisive influence on biochemical thinking.

A recent development of biochemistry, which has made possible the elucidation of the molecular structure and even the synthesis of proteins and enzymes, has also clarified our views about the function of enzymes. The explanation of the fundamental phenomena of life, heredity, and the biosynthesis of proteins controlled by deoxyribonucleic and ribonucleic acids is leading to results which seem really fantastic. This latest development may have some influence also on nutrition research.

The practical goal of the research into nutrition is to elucidate nutritional deficiencies and lack of balance between different food components in man and animals and to find connections between diseases and nutrition. If the idea is accepted in principle that a well-nourished organism is more capable of resisting degenerative diseases, it is logical to suppose that many diseases of this type at the present time are connected with unsatisfactory nutrition.

Although our knowledge about the factors necessary in nutrition has increased tremendously, and it has become possible to give practical instructions for healthy and balanced diets, nutrition in countries where poverty does not restrict the use of food has not developed as favorably as it should have. Above all, the fact that food in these countries has become more and more unbalanced is alarming. Especially, the large amounts of fat in the diet, from 115 to 145 g/day or 35 to 40 % of total calories, deserves special attention.

It is very difficult or even impossible to make such a food well balanced, since the intake of a large amount of fat means, in general, excessive use of energy and fattening, which is a great burden on the organism. The initial stages of the oxidation of fat are of a unique character and may lead to accumulation of ketone bodies. Also combustion of fat is slower than that of carbohydrates.

Major and increasing causes of death in prosperous communities where the use of fat is great are diseases of the circulatory system and the heart. The reason for these diseases has therefore been studied intensively, and a large number of papers have been published in this field

during the last 20 years. The core of the problem has hardly been reached in these studies, but on the basis of them it seems possible that a disturbed lipid metabolism leads to an elevated lipid content of blood—especially cholesterol but also the triglyceride and phospholipid fractions—and as a consequence to atherosclerosis. The formation of thrombi, development of heart infarct, and stroke are results of the damaged circulatory system.

Keys has most vigorously emphasized the connection between the cholesterol content of the blood and atherosclerosis. Many other specialists support this conception, although perhaps not as strictly and clearly as Keys, who thinks that an adequate amount of polyunsaturated fatty acids, especially linoleic acid, nullifies the effect of saturated fatty acids in raising the cholesterol content of the blood. To obtain this goal, a great part of the animal fat in the diet should, according to Keys, be replaced by vegetable oils rich in linoleic acid. The effect of diet low in fat on the development of atherosclerosis has not drawn attention in nutritional studies to the extent it deserves. This type of food may reduce the cases of atherosclerosis.

The desirable reduction of fat in the diet is obstructed by the ever-increasing agricultural production of fat in the developed countries. If this trend in production cannot be totally changed, there will be more and more contrast between production of fat and balanced nutrition.

That the cholesterol and total lipid contents of blood are dependent on the feed used has been strikingly demonstrated in our feeding experiments with cows. When the cows were fed purified nutrients, starch, sugar, and cellulose, using small amounts of vegetable oil, 50–130 g/day, and urea as the sole source of nitrogen, the cholesterol content of blood was exceptionally low, averaging about 50 mg/100 ml, while it was three times as much on normal indoor feeding. Also, the total lipid content of the blood of the cows on the protein-free feed was about one-third of that of normally fed cows. Because of the very low cholesterol content of the blood of the test cows—such values are not known for other adult animals—we have started to study the factors needed to raise the cholesterol and total lipid content of blood to a normal or still higher level.

Dr. Fuson, from Duke University in Durham, North Carolina, last autumn reported that cholestyramine decreases greatly the content of cholesterol and other lipids in the blood. It does not have a direct effect on cholesterol synthesis in the organism, but by functioning as an ion-exchange resin it forms a nonabsorbable complex with bile acids in the intestine and prevents their normal reabsorption from the gut. The result is that the bile acids are excreted in the feces and the fat absorption is also reduced. Because bile acids are formed from cholesterol, the body draws on its cholesterol reserves after cholestyramine administration. Thus all lipid components, especially cholesterol and triglyceride, are strongly decreased in the blood.

Dr. Fuson's experiments with dogs and man have given

very promising results. One must, however, remember that cholestyramine is a drug, and its use is not a natural means to prevent the development of atherosclerosis by using a suitable diet, which must be the goal of nutrition scientists. If the maintenance of the present high fat content of the food is taken as the starting point, real improvement of nutrition will hardly be attained. In this connection one remembers the old story about the custom of the ancient rich Romans to empty their stomachs by vomiting in order to be able to renew the gourmandizing.

There are in prosperous communities individuals and small groups of people who consider the food used completely unwholesome. Vegetarians believe that many of the diseases caused by disturbed metabolism, such as atherosclerosis and cancer, can be prevented by using vegetable food and avoiding the use of animal products. When such food is used, overeating can at least be avoided, but it is very difficult or impossible to make such a food so complete that the intake of all nutritional factors would be ensured. Lacto-vegetarians can receive easily all the necessary nutrients from fruit, vegetables, potatoes, cereals, and milk low in fat. A change toward this type of diet in which a smaller amount of meat can be included would help to prevent present overnutrition.

One of the most important tasks regarding man's nutrition would be to arrange a large-scale experiment in which the influence of some types of diet greatly deviating from one another on man's health, activity, and nervous system would be elucidated. The organization and maintenance of such an experiment, which would last for decades, would demand a great number of scientists and other competent staff as well as plenty of money, but the results of it would show the direction for nutrition of the whole of mankind.

This experiment might illuminate also the following question: is the increasing body size of people using the western type of food advantageous from the viewpoint of man's health and durability, or is the Asian type of man of a small size perhaps more fit to survive in due course of time? Both the daily amount of food and its composition differ very much from each other from east to west. For instance, in Japan, where lately nutritional deficiencies have been removed to a great extent, the food supply per capita is about 70% of that in the United States and in many European countries. In Japan the daily intake of fat is on average only about 45 g as compared with 145 g in the U.S. The proportion of cereals of Japanese food is about 60% of the total calories, while it is about 20% in the U.S. The daily sugar consumption is 46 g in Japan, 110 g in the U.S.

This problem is a very serious one. Experiments with large groups of rats, performed mostly in the United States, have demonstrated clearly that rats consuming food ad libitum grow to big animals, with the average life-span being from 20 to 40% shorter than that of rats on restricted, greatly reduced intake of food and with strongly reduced weight. Ross, who has used more than 1,000 male rats in his feeding experiment says in his

paper of 1961: "From the data presented, life-span is definitely a function of the lifelong dietary regimen."

In poor countries suffering from lack of food, nutritional problems differ essentially from those in developed countries. The great problem of large sections of poor people is how to get some food to appease hunger. Ignorance, apathy and, in general, the lack of activity contribute to the nutritional difficulties. Under these circumstances malnutrition cannot be avoided. The lack of protein of high quality, especially, leads to malnutrition in these countries. The excellent quantitative studies of Rose, at the University of Illinois, about the amino acid requirements of rat and man have made it possible to determine the biological value and the daily requirements of various proteins. According to Food and Agriculture Organization statistics, at least half of mankind suffers from protein deficiency, mostly owing to the inadequate composition of the protein found in cereals. The situation is most difficult with children, who need exceptionally large amounts of essential amino acids for the growth of the tissues. Damage caused by the lack of protein during childhood cannot be remedied later, at least not completely. Peoples suffering from the lack of protein are thus in a witch's cage from which it is difficult to escape.

Many plans for the removal of the protein deficiency of undernourished peoples have been made during the last few years. Great attention has been paid to entirely new methods for protein production. The chemical industry has developed syntheses of amino acids, which are present in cereals in too low concentrations. Lysine particularly has hereby the key position. The synthesis of L-lysine on a large scale has succeeded so well that the price no longer prevents its addition to flour. The prices of synthetic DL-tryptophan and DL-threonine are still too high to permit their general use. The difficult problem is how the addition will be possible when millions of small farmers produce the cereals they consume themselves. In any case, the industrial production of amino acids needed for supplementation of cereals has given a theoretical possibility to improve the nutritional value of flour. Howe and associates have recently discussed this problem in the *American Journal of Clinical Nutrition*.

The cultivation of unicellular green algae in inorganic nutrient solution has been the object of very great attention. In green algae, more than half of the dry matter is protein and, because they give very high yields in sunny, warm areas under favorable nutritional conditions, it was supposed that protein deficiency could be removed by mass cultivation of these organisms.

The matter is not simple, however, due to several reasons. First, the separation of algae from nutrient solutions is a difficult task, which is not yet economically solved, and second, the utilization of protein of a fresh mass of algae is only 25%. The utilization is radically improved only when the cell walls are broken, which takes place at a high temperature. The biological value of the protein of roller-dried algae is about 90% that of casein. All these difficulties mean that very cheap protein

cannot be produced in this way. Dr. H. Kraut, from Kohlenstoffbiologische Forschungsstation in Dortmund, West Germany, has recently compared his own results with those obtained in Japan and Israel.

A new means for the production of protein by cultivating suitable yeast species, which utilize as organic nutrient certain *n*-paraffin hydrocarbons found in petroleum, has been vigorously advocated during this decade. The method has been developed on a pilot plant scale in Laverne, France. The first data were indeed startling. At a high oxygen concentration, the yeast grown in the water phase of an oil-in-water emulsion in direct contact with oil droplets utilizes energy-rich hydrocarbons effectively, giving great yields. Thus it was believed that it would be possible to produce for the nutrition of man gigantic amounts of protein-rich yeast in conjunction with the petroleum industry. It seems, however, that the first yeast factory, which British Petroleum is now building, will produce fodder yeast for pigs and poultry. The process uses a cheap gas-oil refinery fraction which contains only 10% *n*-paraffins. The yeast protein would also in this case be utilized by man via domestic animals.

Sensational news has quite recently appeared in the newspapers about the cultivation of special bacteria with methane gas as carbon nutrition and source of energy. Although it is not a new idea, its realization as an industrial process is still questionable. The problem, as well as yeast production on petroleum, was dealt with at the Second International Conference on Global Impacts of Applied Microbiology in Addis Ababa last November, according to a report in the *New Scientist*.

The possibilities of obtaining protein-rich food from the oceans have been dealt with by many authors. At present hardly anything else can be said except that fishing will increase, especially for small fish of low commercial value. It is improbable that in the near future any basically new method, as for example collecting of plankton, will come into practice.

In the field of conventional agriculture, results have been obtained during the last few years which show the capability of this basic occupation of man to develop new methods in case of need. A strain of maize, *opaque-2*, was found by Mertz, Bates, and Nelson in 1964 to be exceptionally high in lysine and later on in tryptophan, too. In addition, the new strain had a better balance between leucine and isoleucine than other hybrid strains. Experiments with animals, children, and adults have given results about the nitrogen balance which are in agreement with the amino acid composition of the protein of *opaque-2*. About 300 g of this maize are needed to maintain a good protein status in the adult. The use of this maize strain in the areas where maize is cultivated would bring decisive improvement in the protein situation provided the yield is also high. Unfortunately maize is a rather demanding plant which is not suitable for cultivation in wide areas of the globe. There is, however, some work in progress with other grain crops.

On the basis of experiments in the field of cattle feed-

ing, true protein in the feed can be replaced largely by urea. At the Biochemical Research Institute in Helsinki I have been especially interested in the nitrogen nutrition of dairy cows because both the energy and protein efficiency of the feed for milk production are much higher than those for meat production. On the other hand, the daily milk production of good dairy cows is so high that plenty of protein is needed in the daily ration of a milking cow. Accordingly, feeding experiments with milking cows on synthetic protein-free feed make it possible to get information on the capacity of the ruminal flora to synthesize microbial protein from nonprotein nitrogen. In our feeding experiments performed during the last 6 years with Ayrshire cows of an average weight of about 450 kg, we have demonstrated that considerable milk yields can be produced on a protein-free feed composed of purified nutrients, starch, cellulose, and sugar, with urea and a small amount of ammonium salts as the sole source of nitrogen. A yield of more than 4,000 kg of milk/year has been reached on such a feed. The composition of the milk produced, called "zero milk" in our laboratory, is similar to that of milk produced on normal feed. In the investigations special attention has been paid to the proteins, flavor substances, water-soluble vitamins, and lipids of the milk.

In experiments of a practical nature on feed very low in protein, the annual milk yield per cow has been

5,000–6,000 kg. The portion of digestible true protein in the feed was 20 and 40 % of the digestible crude protein when the digestible urea nitrogen was 65 % and 53 %, respectively. On the basis of our results entirely new possibilities are opened for milk production, especially in areas where no protein-rich feed is available. By replacing a considerable part of proteins with urea in countries with developed dairying, enormous amounts of seed proteins, especially from soybeans and cottonseeds, would be released for man's nutrition in underdeveloped areas. New carbohydrate sources, such as hemicellulose from wood, can now be used for milk production.

This is very important, because the lack of energy nutrition prevails often in the same areas where people suffer from malnutrition due to protein and vitamin deficiency. The feeding of urea to the extent used in our experiments makes possible the use of an extremely protein-poor feed for milk production.

Many new means for the production of protein are developing at present. New observations regarding the raising of the biological value of cereal proteins, as well as the use of nonprotein nitrogen in milk and meat production, will open new possibilities for agriculture and cattle husbandry for the prevention of protein deficiency—possibilities which will reach the widespread areas of poverty in underdeveloped countries.